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A longitudinal study assessing depression in hepatitis C: Does gender play a role in the new-onset depression during interferon-alpha treatment?

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Abstract

In this prospective study conducted from October 2013 to June 2015 in Brighton, England, we examined differences between men and women in new-onset major depressive disorder (MDD) during interferon-alpha-based (IFN-α) therapy for hepatitis C virus (HCV). We included 155 HCV-infected patients (47 women), eligible to receive HCV therapy, including direct-acting antivirals. The Semi-Structured Clinical Interview (SCID-I) was used to assess MDD. Severity of depressive symptoms was assessed using the Hamilton Depression Rating Scale. Patients were assessed at baseline, during treatment and six months after treatment completion. A significant increase in depressive symptoms was observed in the total sample from baseline to week 4, and a significant decrease was observed from end of treatment (week 24) to the sustained virological response (SVR) endpoint at six months post-treatment. Women were more likely to have a MDD at week 24. In both men and women, neuro-vegetative and mood-cognitive syndromes increased significantly at the early stage of treatment but remitted by the end of HCV therapy. Proportions with SVR was similar among females and males (91.5% vs. 87%). Under an inflammatory condition, boosted by interferon-based treatments, these results suggest that female gender is not associated with increased vulnerability for developing depression during IFN-α therapy.

Keywords**:** depression; hepatitis C; gender differences; interferon-alpha; direct-acting antivirals

Introduction

The prevalence of hepatitis C virus (HCV) is high worldwide, and HCV infection remains the leading cause of liver disease (Mohd Hanafiah et al. 2013). The transmission of HCV has been consistently associated with intravenous drug use (IDU) and high-risk sexual practices, particularly together with recreational drug use (Ryder 2015). Most studies in this field have, however, been based on predominantly male samples, leaving HCV-infected women inadequately represented in research. This limits the understanding of potentially important gender differences in response to HCV treatment, particularly the neuropsychiatric effects associated with interferon-based treatments.

A recent prospective study suggested that women were more likely than men to become infected with HCV and to report a high risk of injecting behaviors when in a sexual relationship with an IDU partner (Tracy et al. 2014). Among women, substance abuse, HIV infection, and age over 35 years have been identified as risk factors for HCV (Operskalski et al. 2008). These findings highlight the relevance of gender in the context of hepatitis C, which is particularly reinforced by recent meta analytic data indicating that among HCV-infected women the risk of perinatal infection transmitted to offspring was 5.8% [95% confidence interval (CI), 4.2%-15.2%], and that the risk of vertical transmission of HCV is increased among women, with 1 in every 20 children of a mother with chronic HCV infection being infected (Benova et al. 2014; Buchanan and Nash 2015).

Direct-acting antivirals (DAAs) with pegylated-interferon and ribavirin, and interferon-free regimens have emerged as the new treatment options for HCV. Despite the emergence of interferon-free regimens, the pegylated-interferon and ribavirin-based treatment is still a valid option, with high cure response rates in acute and chronic HCV infection (Feld 2012). In relation to sex differences, although the research has been rather limited, existent evidence about the effectiveness of interferon-based treatment is mixed, with reports of lack

of differences between males and females in the response to HCV treatment (Hayashi et al. 1998; McHutchison et al. 2009), but also of lower (Akuta et al. 2007; Villa et al. 2011) and higher (Conjeevaram et al. 2006; Grebely et al. 2014) rates of sustained virological response (SVR) among women. Recent data on DAAs indicated absence of significant differences between men and women in response to treatment with telaprevir and bocepravir (Jacobson et al. 2011; Poordad et al. 2011). Another study found that women presented a poorer response to treatment (Simoes et al. 2015).

The combination of interferon-alpha (IFN-α) and ribavirin has often been associated with psychiatric side effects, which have a significant negative impact on patients' quality of life and treatment compliance and are risk factors for treatment failure. In this context, major depressive disorder (MDD) has been reported as one of the most frequent psychiatric side effects in the context of interferon-based therapy for HCV (Schaefer et al. 2012). During HCV treatment, increased levels of depressive symptoms have been reported (Udina et al. 2012), particularly at earlier stages of treatment. Moreover, it has been suggested that patients with IFN-induced depression show significantly more symptoms of the neurovegetative syndrome than mood-cognitive symptoms (Capuron et al. 2009). However, if this is true for both men and women with hepatitis C remains to be explored.

In the the non-iatrogenic model of depression, women have higher rates of depression than men (Kessler et al. 1993; Romans et al. 2007), particularly for bipolar depression (Parker et al. 2014; Piccinelli and Wilkinson 2000). In the general population, evidence also suggests that women develop depression at an earlier age and experience more depressive episodes than men (Azorin et al. 2014), which has been related to a multifactorial model, composed of several vulnerability factors, such as childhood sexual abuse, parental loss or disturbed family dynamics, neuroticism traits, early onset of anxiety disorders, substance abuse, low social support and negative life events (Kendler et al. 2002; van Loo et al. 2015).

Interestigly, concerning the inflammatory model of depression, such gender vulnerability has not been confirmed. Recently, when examining the biopsychosocial effects of IFN-α treatment of patients with chronic hepatitis C, Baranyi et al. (2013) found that more patients with treatment-induced depressive symptoms were female, and regarding the neurotoxic challenge (kynurenine to kynurenic acid quotient) and the tryptophan (TRP) availability to the brain, gender was not a significant factor. In a meta-analysis with 845 patients undergoing IFN-based treatment, female gender was a weak risk factor for the emergence of IFN-induced depression (Udina et al. 2012), although this finding was not confirmed in a recent study by Whale et al. (2015), which found that gender was not a significant risk factor for the emergence of MDD in a cohort of patients with HCV infection during IFN-α treatment. However, these studies did not focus on the clusters of depressive symptoms (neurovegetative and mood-cognitive), across HCV treatment as described by previous reports (Capuron et al. 2009).

As mentioned above, HCV-infected women are an underepresented population in HCV studies, and specific data during hepatitis C treatment are limited. In addition, although a number of studies have assessed new-onset depression during treatment, understanding of depression during HCV treatment among women is still limited. Understanding the psychiatric side effects during treatment in this population is clinically relevant for carefully planning treatment options and implementing tailored interventions for patients with hepatitis C. Gender sensitive services also need to be considered to address prevention of new HCV infections, mental health comorbidities, as well as unique features of the female population, such as vertical transmission of HCV and menopausal issues. Therefore, the aim of this prospective study was to explore gender differences in new-onset MDD (defined as the development of depression during treatment among patients who were not depressed prior to the initiation of treatment) during hepatitis C treatment, to identify factors associated with

development of MDD during treatment, and, additionally, to examine longitudinally the existence of gender differences in the expression of subtypes of depressive symptoms.

Methods

Participants and procedure

Based on the National Institute for Health and Care Excellence (NICE), the national clinical guidelines for hepatitis C treatment were followed to identify the participants eligible for treatment. A cohort of 231 patients eligible for HCV treatment were consecutively recruited between October 2013 and June 2015 at the outpatient HCV clinic at the Royal Sussex County Hospital, Brighton UK. Eligibility criteria for treatment were based in clinical assessment investigations with the combination of blood tests results (HCV antibody positivity) and liver ultrasound to identify the stage of liver disease, acute or chronic stage of HCV infection, and HCV genotype. Circulating HCV RNA was confirmed by reverse transcription polymerase chain reaction. Patients were included both with previous and with no history of IFN-α treatment. All HCV genotypes were included. The following exclusion criteria were considered: being re-infected with HCV, co-infection with HIV, autoimmune disorder or any cause of liver disease other than HCV, history of neurological disease, acute psychiatric illness, current diagnosis of MDD, being on methadone, and intravenous drug or alcohol abuse within the month prior to the beginning of hepatitis C treatment. Of the 231 participants enrolled in the study, 15 (6.5%) were excluded from the study analyses because of HCV re-infection episodes, 37 (16%) because of HIV co-infection, five (2.2%) due to current drug use and 19 (8.2%) due to baseline MDD. The final sample consisted of 155 participants (retention rate = 67.1%).

All participants were eligible to start hepatitis C treatment with interferon-based therapies: a combination of PEG-IFN 2α 180 μg weekly sub-cutaneously and oral ribavirin 800-1200mg daily (depending on weight and HCV genotype) or these two medications

(PEG-IFN 2α 180 μg weekly sub-cutaneously and oral ribavirin 800-1200mg daily) plus protease inhibitor telaprevir orally (750 mg) every 8 hours. Only those exposed to 24 weeks of treatment were included. All participants were evaluated at multiple time points within the study period: baseline, week 4, week 12, week 24, and six months after treatment completion (SVR endpoint).

All participants were informed about the aims of the study and gave written informed consent for participation. Ethical approval was obtained for the study protocol through the National Research Ethics Service (NRES) Committee South East Coast.

Measures

At the baseline assessment, sociodemographic data (e.g., age, gender, marital status), HCV-related variables (e.g., route of HCV infection, HCV stage, genotype, HCV therapy), and information related to past psychiatric history, and past drug use was collected. Positive response to treatment (viral clearance) was measured by SVR, defined as negative HCV viral load measured by polymerase chain reaction assay (PCR, HCV RNA < 1.9 log IU/mL) six months after treatment completion.

The diagnosis of MDD was determined through a semi-structured clinical interview (SCID-I) (First et al. 1996) for the major DSM-IV Axis I diagnosis. For the purpose of defining a depression threshold, criterion A12D of the SCID-I (excluding other organic etiologies) was discarded. Severity of depression and sub-syndrome features were assessed with the 21-item Hamilton Depression Rating Scale (HAMD) (Hamilton 1960), which consists of 21 items answered on a three-point (0-2), four-point (0-3) or five-point (0-4) response scale. The total score ranges between 0 and 66, and higher scores denote higher severity of depressive symptoms. This study adopted the factor structure suggested by Capuron et al. (2009): (1) depressive symptoms (depressed mood, feelings of guilt and suicide items); (2) anxiety symptoms (anxiety psychological, hypochondriasis, agitation and

anxiety somatic items); (3) impaired activity (work/activities and retardation); (4) sleep alterations (early, middle and late insomnia items); and (5) somatic symptoms (somatic symptoms gastrointestinal, somatic symptoms general, genital symptoms and loss of weight). For the present study, these factors were combined into a dichotomous model of depression: the neurovegetative syndrome, which was composed by impaired activity, sleep alterations and somatic symptoms; and the mood-cognitive syndrome, which combined depressive and anxiety symptoms. Alpha reliability in this sample ranged between 0.82 (Baseline, for men) to 0.95 (SVR, for men).

Data analysis

Participants were individually coded for either transition to MDD (new-onset depression, defined as development of MDD during treatment among patients who were not depressed prior to the initiation of treatment) or no transition to MDD at any time point during this period. Descriptive statistics with means and standard deviations (*SD*) were reported for continuous variables, and frequencies for categorical variables. Characteristics were compared with Student's *t* tests for continuous variables, and χ^2 test and Fisher's exact test as appropriate, for testing differences in categorical variables. Repeated-measures multivariate analysis of covariance (MANCOVA) was used to assess changes in depressive symptoms subtypes across groups (between-patients; female vs. male) and over time (within-patients). Factors significantly associated ($p < 0.05$) with increased odds of developing MDD during HCV treatment (past psychiatric history, past drug use and type of HCV treatment) and anti-depressant treatment, which was defined a priori as a potential confounder, were included as covariates. The criterion Wilks' Lambda was used to assess the significance of the effects (Tabachnick and Fidell 2013). Subsequent univariate analyses of covariance (ANCOVA) were performed to identify the source of the multivariate effects. Bonferroni adjustments were applied to correct for multiple comparisons ($p < 0.01$). Logistic regression

analyses were used to identify factors associated with development of MDD during treatment. The goodness-of-fit of the logistic regression models was evaluated using the Hosmer-Lemeshow test, with lower values (and non-significance) indicating a good fit to the data. The statistical significance of individual factors was assessed by calculating the odds ratio (OR) with a 95% confidence interval (CI). Effect sizes were calculated for all analyses (small effects: Cohen's $d \geq 0.20$, Cramer's $V \geq 0.10$; medium effects: Cohen's $d \geq 0.50$, Cramer's $V \geq 0.30$; large effects: Cohen's $d \geq 0.80$, Cramer's $V \geq 0.50$) (Cohen 1992). Data were analyzed using the Statistical Package for Social Sciences (IBM SPSS, version 20.0).

Results

Participants' characteristics

The final sample consisted of 155 patients (30.3% female; $n = 47$). The mean age was 47.66 years ($SD = 9.79$; range: 27-66 years) for females and 46.61 years ($SD = 10.66$; range: 25-71 years) for males (Table 1). The majority of females were married or cohabiting (53.2%), while males were mostly single (48.1%) or married/cohabiting (44.4%). Most patients had chronic HCV infection (84.5%; 87% for females and 78.7% for males), and 49% were infected with genotype 2 virus (51.1% for females and 48.1% for males). The majority of patients reported past drug use (68.1% for females and 67.6% for males) and IDU as route of HCV infection (63.8% for females and 63.9% for males).

Regarding treatment, 69% of patients received pegylated INF-α and ribavirin (72.3% for females and 67.6% for males). Sixty-nine (44.5%; 53.2% for females and 40.7% for males) patients reported past psychiatric history, out of which 59 (85.5%) specified prior history of depression. Most patients were not on anti-depressant treatment (61.7% for females and 64.8% for males). A SVR response was achieved in 88.4% of the sample (87% for females and 91.5% for males). No significant differences were found between male and female patients in the baseline study variables.

Depressive symptoms at baseline

In the total sample, the mean HAMD total score at baseline was 3.17 (*SD* = 4.53; range: 0-22). No significant differences were found between females (*M* = 3.13, *SD* = 4.66) and males (*M* = 3.19, *SD* = 4.50) regarding baseline HAMD total score, $F(1, 154) = 0.01$, $p = 0.933$.

Development of MDD during treatment

A total of 73 patients (47.1%) developed SCID-I defined MDD during HCV treatment. Of those identified with MDD, 35 patients developed MDD by week 4, and 55 patients were diagnosed with MDD by week 12. These findings represent a cumulative percentage of 75.3% of patients developing MDD within the first 12 weeks of treatment. A higher proportion of women developed MDD during treatment (53.2% vs. 44.4%), although the difference was not statistically significant, $\chi^2_{(1)} = 1.01$, $p = 0.316$, Cramer's $V = 0.08$.

When examining the gender differences in the diagnosis of MDD in each time point (Table 2), the results indicated that females were not more likely than men to be diagnosed at week 4 (23.4% vs. 22.2%; $\chi^2_{(1)} = 0.03$, $p = 0.871$, Cramer's $V = 0.01$) or at week 12 (44.7% vs. 31.5%; $\chi^2_{(1)} = 2.49$, $p = 0.114$, Cramer's $V = 0.13$). However, being female was significantly associated with higher odds of having a MDD diagnosis at week 24 (42.6% vs. 23.6%; $\chi^2_{(1)} = 5.64$, $p = 0.018$, Cramer's $V = 0.19$).

Factors associated with development of MDD: Preliminary analyses

A range of preliminary analyses (univariate logistic regressions) examining the association between baseline factors and new-onset depression during HCV treatment was conducted in the total sample and separately by gender. For the total sample, the results indicated that having past psychiatric history (OR 2.47, 95% CI 1.29-4.73, $p = 0.006$) was

significantly associated with increased odds of developing MDD during treatment. Also, past drug use was associated with the development of MDD only for women (OR 5.25, 95% CI 1.35-20.40, $p = 0.017$). Being on triple therapy (interferon plus ribavirin plus telaprevir) was significantly associated with lower odds of developing MDD only among men (OR 0.37, 95% CI 0.16-0.88, $p = 0.024$). Thus, in the analyses of the changes in the severity of symptoms of depression during treatment, the results were adjusted for these potential covariates, along with anti-depressant treatment, which was defined a priori as a potential confounder.

Changes in depressive symptoms during HCV treatment

Regarding the HAMD total score, the results of the repeated measures MANCOVA (adjusted for past psychiatric history, past drug use, type of HCV treatment, and anti-depressant treatment) indicated a significant effect of time [Wilk's $\lambda = 0.74$, $F(4, 146) = 13.60$, $p < 0.001$, $\eta_p^2 = 0.26$]. Neither the effect of group [$F(1, 149) = 0.18$, $p = 0.666$, $\eta_p^2 = 0.001$] nor the interaction of time x group [Wilk's $\lambda = 0.99$, $F(4, 146) = 0.01$, $p = 0.876$, $\eta_p^2 = 0.01$] were significant. Regarding the effect of time, subsequent analysis indicated a significant increase in HAMD total score from baseline to week 4 (Mean difference = 9.49, $p < 0.001$), and a significant decrease between week 24 and the SVR endpoint (Mean difference = 12.10, $p < 0.001$). The increases in depressive symptoms from week 4 to week 12 and from week 12 to week 24 were not statistically significant (see Figure 1). No significant differences were observed between men and women in the changes of the HAMD total score during treatment.

Regarding the two syndromes of depressive symptoms, while adjusting for the same covariates, the results indicated a significant effect of time [Wilk's $\lambda = 0.18$, $F(8, 142) = 79.05$, $p < 0.001$, $\eta_p^2 = 0.82$]. The effect of group [Wilk's $\lambda = 0.98$, $F(2, 148) = 1.88$, $p =$

0.157, $\eta_p^2 = 0.03$] and the interaction between time and group were not significant [Wilk's $\lambda = 0.97$, $F(8, 142) = 1.54$, $p = 0.766$, $\eta_p^2 = 0.03$] (Table 3). Follow-up tests showed a significant increase in both mood-cognitive and neurovegetative syndromes during treatment, most notably between baseline assessment and week 4 ($p < 0.001$). Additionally, a significant decrease in both syndromes between week 24 and SVR endpoint was found (all $p < 0.001$, Figure 2).

Discussion

In this prospective study, we found a significant increase in depressive symptoms from baseline to week 4 of treatment and a significant decrease from week 24 to the SVR endpoint, a pattern that was similar for both men and women. When examining the association between gender and new-onset MDD in each time point of the study, we found that women were more likely than men to have a diagnosis of MDD at the end of treatment (week 24). During interferon-based therapy, dimensional analyses of depressive symptoms developing during treatment also indicated a similar time course for men and women, that is, a significant increase in neurovegetative and mood-cognitive syndromes at the beginning of the therapy, notably at week 4 and a remission after the end of treatment. The rate of treatment response (SVR) was high in the overall sample (88%), with no differences between men and women.

For both men and women, the severity of depressive symptoms was high at the beginning of treatment and remitted after exposure to treatment, as reported in prior studies (Huckans et al. 2015; Loftis and Hauser 2004) and confirming the transient depressogenic nature of IFN-α. Our findings also indicated that women were more likely to present with MDD at week 24 when compared to men (no differences were found in the remaining time points, however). Although a recent meta-analytic data of ten studies suggested that female gender was a (weak) predictor of new-onset depression during HCV treatment (Udina et al.

2012), all studies included in this meta-analysis did not find evidence of differences between men and women (although a trend was observed for women reporting higher odds of occurrence of interferon-alpha-induced depression). To some extent, our findings are consistent with the studies reported in this meta-analysis indicating a lack of differences between men and women in new-onset depression.

Evidence suggests that residual symptoms, early adverse life events and previous episodes of depression are risk factors for recurrence of MDD (Hardeveld et al. 2013; Nanni et al. 2012; van Loo et al. 2015). The presence of MDD at later stage of HCV treatment in the female sample may relate to the level of residual symptoms that have increased the likelihood of subsequent MDD symptoms, particularly given that more than 50% of women of this sample reported past psychiatric history. Moreover, the kindling hypothesis suggests that the risk of subsequent MDD may depend on the level of stress exposed to (Kendler et al. 2000). Experiencing interferon-based therapy may induce high levels of stress, thus enhancing MDD.

The preliminary analyses indicated that past psychiatric history, past drug use (only for women) and being on triple therapy (only for men) were significantly associated with new-onset depression during HCV treatment. The finding regarding past psychiatric history is not surprising, as general psychiatric history has been often identified as a reliable risk factor for new-onset depression during interferon-based therapy (Udina et al. 2012). Although past drug use was not associated with an increased risk of IFN-induced MDD in previous studies (e.g., Hauser et al. 2002), having past or current drug misuse is a well-known psychosocial vulnerability factor among HCV patients (Asnis and De La Garza 2006). Gender has also been regarded as a significant vulnerability factor for depression (Kessler et al. 1993; Schuch et al. 2014), and a recent meta-analysis revealed female gender to be associated (weak effect) with depression emergence during IFN-α treatment (Udina et al.

2012). Thus, it is possible that these factors, cumulatively, may have increased the risk of developing depression during HCV treatment. In contrast to a recent study (Belvederi Murri et al. 2017), our findings indicated that being on triple therapy was significantly associated with lower odds of developing MDD, but only for male patients. Evidence suggested higher SVR rates among patients on triple therapy compared with those on a standard regimen of pegylated interferon and ribavirin (e.g., Jacobson et al. 2011). The addition of protease inhibitors could also shorten therapy without loss of efficacy (Hullegie et al. 2015).Thus, it is possible that achieving viral clearance in a shorter period of time may have reduced the state of inflammation and, consequently, inhibited the emergence of MDD. Yet, the gender difference is unknown. We acknowledge, however, that our sample size may have provided insufficient statistical power to draw more solid conclusions. Therefore, future studies should undertake investigation of gender differences in development of MDD for the different treatment modalities using a sufficient sample size to investigate this important issue.

Regarding the dimensional analyses of depressive symptoms developing during treatment, we found that mood-cognitive and neurovegetative syndromes significantly increased at the beginning of treatment, a pattern that was similar for males and females. The neurovegetative syndrome typically occurs within the first month of treatment (Loftis et al. 2013), being less responsive to antidepressant treatment (Capuron and Miller 2004). These symptoms are exhibited preferentially with IFN-α therapy, suggesting that IFN-α causes a dysregulation of the cytokine network that may involve basal ganglia changes and dopamine depletion (Capuron et al. 2007, 2009, 2012; Hayley et al. 2013; Wichers et al. 2007). The emergence of the mood-cognitive syndrome at the early stage of treatment is not consistent with previous findings showing that this syndrome occurs later in treatment (Capuron et al. 2002).

IFN-induced mood-cognitive syndrome may involve abnormalities in tryptophan/serotonin metabolism (Capuron et al. 2002; Raison et al. 2010). This suggests that IFN-α activates different pathophysiological mechanisms causing two different behavioral syndromes. What is unclear is why the mood-cognitive syndrome develops only in a smaller proportion of patients (Capuron et al. 2007; Musselman et al. 2001). Another explanation might be associated with the overlap effects of emotional adjustment to HCV treatment that often combines symptoms of anxiety and depression, as assessed by the HAMD. The early emergence of these symptoms in treatment suggests that the beginning of treatment is crucial for a comprehensive monitoring and clinical supervision.

This study was not without limitations, which must be considered when interpreting the findings. First, the convenience sampling from a single hospital and the relatively small sample size of the female group means that the results may not be generalizable, and any such generalization should be undertaken with great caution. Second, despite the inclusion of several sociodemographic and HCV-related variables, it would have been useful to have added other variables (e.g., inflammatory markers, such as IL-6 and CRP) that have been associated with depression (Krogh et al. 2014). Recent evidence has also indicated that quinolinic acid during IFN-α treatment may have a key role in the emergence of depressive symptoms through the neurotoxic challenge caused by the increase of quinolinic acid (Baranyi et al. 2015). Thus, our results may reflect residual confounding. Therefore, the inclusion of information pertaining to these relevant variables in future studies could provide us a better understanding of the nature of IFN-induced depression. Finally, the lack of inclusion an untreated control group did not allow us to determine if the increase in depressive symptoms could be attributed to HCV treatment.

Despite these limitations, this study has also important strengths. To our knowledge, this is the first study reporting a detailed assessment of neuropsychiatric side effects in a

female sample during HCV treatment. The study design was prospective and longitudinal, and all patients were followed in a single center. In addition, this study used both a validated measure for assessing the severity of depressive symptoms (which is useful for examining individual symptoms and changes over time) and a clinical interview based on DSM criteria conducted by a trained clinical psychologist.

In summary, in this study, a high rate of MDD was observed during HCV treatment. Women were more likely to present MDD at a later stage of treatment, which may be related to vulnerability factors, such as past psychiatry history and past drug abuse. Neurovegetative and mood-cognitive syndromes stood out as significantly higher at the beginning of the treatment, and both remitted at the end of treatment, indicating that these symptoms have a temporary effect caused by the interferon exposure. The persistence of depressive symptoms in the female sample (still present at week 24) may have been attributable to a more severe past history of risk factors. With interferon-free regimens, gender differences are unlikely to be seen, however, because the onset of a MDD episode and recurrence depends on multifactorial model characterized by a complex interplay between biological, psychological and environmental factors (Kendler and Gardner 2014), before starting treatment, it would be valuable to conduct a full assessment of well-established risk factors for new-onset depression. This screening is crucial to decrease the risk of depression and improve treatment compliance and the well-being of this population.

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Table 1. Demographic and clinical characteristics of patients receiving HCV treatment by sex ($N = 155$)

	Total ($n = 155$)	Female ($n = 47$)	Male ($n = 108$)	χ^2	Cramer's V
	n (%)	*n* (%)	*n* (%)		
Marital status				1.29	0.09
Single	70 (45.2)	18 (38.3)	52 (48.1)		
Married/Cohabiting	73 (47.1)	25 (53.2)	48 (44.4)		
Separated/Divorced	12 (7.7)	4 (8.5)	8 (7.4)		
HCV stage				1.73	0.11
Acute	24 (15.5)	10 (21.3)	14 (13.0)		
Chronic	131 (84.5)	37 (78.7)	94 (87.0)		
Route of HCV infection				0.00	0.001
IDU	99 (63.9)	30 (63.8)	69 (63.9)		
Non-IDU	56 (36.1)	17 (36.2)	39 (36.1)		
Genotype				2.32	0.12
1	52 (33.5)	15 (31.9)	37 (34.3)		
2	76 (49.0)	24 (51.1)	52 (48.1)		
3	16 (10.3)	3 (6.4)	13 (12.0)		
4	11 (7.1)	5 (10.6)	6 (5.6)		
HCV treatment				0.35	0.05
PEG-IFN 2α +Ribavirin + Telaprevir	48 (31.0)	13 (27.7)	35 (32.4)		
PEG-IFN 2α + Ribavirin	107 (69.0)	34 (72.3)	73 (67.6)		
Past psychiatric history				2.06	0.12
No	86 (55.5)	22 (46.8)	64 (59.3)		
Yes	69 (44.5)	25 (53.2)	44 (40.7)		
Past drug use				0.04	0.01
No	50 (32.3)	15 (31.9)	35 (32.4)		
Yes	105 (67.7)	32 (68.1)	73 (67.6)		
Antidepressant treatment during therapy				0.14	0.03
No	99 (63.9)	29 (61.7)	70 (64.8)		
SVR				0.63	0.06
Yes	137 (88.4)	43 (91.5)	94 (87.0)		
	Mean (*SD*)	*Mean* (*SD*)	*Mean* (*SD*)	*t*	Cohen's *d*
Age	46.93 (10.38)	47.66 (9.79)	46.61 (10.66)	-0.58	0.10

*** $p < 0.001$

Table 2. Development of SCID-I defined MDD by week of HCV treatment and by sex (N = 155)

		Week 4	Week 12	Week 24	SVR
Female					
MDD - Yes	*n*	11	21	20	2
	%	23.4	44.7	42.6	4.3
Male					
MDD - Yes	*n*	24	34	25	6
	%	22.2	31.5	23.6	5.6
Total					
MDD - Yes	*n*	35	55	45	8
	%	22.6	35.5	29.4	5.2

Table 3. Descriptive statistics in HAMD factors during interferon-based therapy for HCV

	Baseline	Week 4	Week 12	Week 24	SVR	Time (*F*)	Group (*F*)	Time X Group (*F*)
	Mean (*SE*)	*Mean* (*SE*)	*Mean* (*SE*)	*Mean* (*SE*)	*Mean* (*SE*)			
Mood-Cognitive syndrome						4.42**	1.41	0.98
Female	0.17 (0.04)	0.52 (0.07)	0.67 (0.07)	0.60 (0.08)	0.02 (0.02)			
Male	0.17 (0.02)	0.48 (0.05)	0.57 (0.05)	0.47 (0.05)	0.03 (0.02)			
Neurovegetative syndrome						19.64***	0.26	0.12
Female	0.19 (0.04)	0.85 (0.07)	0.96 (0.07)	0.86 (0.08)	0.03 (0.03)			
Male	0.20 (0.03)	0.91 (0.05)	0.98 (0.04)	0.85 (0.05)	0.05 (0.02)			

** $p < 0.01$; *** $p < 0.001$

Figure 1. Time course of HAMD total depression score in HCV mono-infected male and female patients during HCV treatment

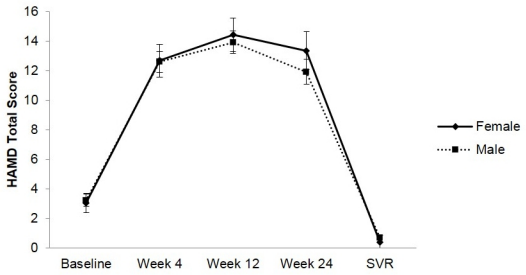

Figure 2. Time course of HAMD clusters of depressive symptoms in HCV-infected men and women during HCV treatment